STUDY OF THE IMPURITY PROFILES OF SOME MARKETED FORMULATIONS DURING STABILITY EVALUATION IN DIFFERENT PRIMARY PACKAGING

SYNOPSIS OF THE THESIS

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In Partial Fulfillment of Requirements

For the degree of

DOCTOR OF PHILOSOPHY

SCHOOL OF PHARMACY

FACULTY OF PHARMACY

ABHILASHI UNIVERSITY

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FEBRUARY 2019

.DECLARATION

I hereby declare that the dissertation synopsis entitled "*Study of the impurity profiles of some marketed formulations during stability evaluation in different primary packaging*" to be submitted for partial fulfillment of degree of Doctor of Philosophy is my original work and the dissertation has not formed the basis for the award of any degree, diploma, associateship or fellowship of similar other titles. It has not been submitted to any other University or Institution for the award of any degree or diploma.

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Chapter 1
Introduction

1. INTRODUCTION

1.1 Stability study.

The quality of an active pharmaceutical ingredient (API) or finished pharmaceutical product (FPP) is quite prone to variation with the lapse of time. There is a number of factors that affect the effectiveness of a drug. These include environmental factors -temperature, humidity, and light on one hand whereas product-related factors like- the interaction of active pharmaceutical ingredient with excipients, packaging materials, and container closure systems on the other hand. Stability study programs help to determine such effects. Stability testing helps to determine the shelf-life for the drug product and also to recommend storage conditions. In exceptional cases where the formulation includes unstable active pharmaceutical ingredients, a re-test period for the active pharmaceutical ingredient is recommended. [1]

1.1.1 Study of Stability at various stages

1. Accelerated and Stress testing -with drug substances.
2. Pre-formulation batches. -Stability testing
3. Stress testing on scale-up Batches.
4. Long term and Accelerated testing for registration.
5. Continuous Stability testing.
6. Stabilities.

1.1.2 Climatic Zones.

Table.1: Different Climatic Zone as per ICH guidelines.

Climatic Zone	Countries	Calculated Data			Derived Data	
		Temp	MKT	RH %	Temp	RH %
Zone I **Temperate**	United Kingdom, Japan, Northern Europe, Canada, Russia	20	20	42	21	45
Zone II	Japan, United	21.6	22	52	25	60

Mediterranean Subtropical	State, Southern Europe					
Zone III Hot Dry	Iran, Iraq, Sudan	26.4	27.9	35	30	35
Zone IV Hot Humid	Brazil, Ghana, Philippines	26.4	27.4	76	30	70

1.1.3 ICH Guidelines [2]

ICH guidelines compose a comprehensive set of scientific rules on human medicines to achieve harmonization at a worldwide level. It is a committee -International Council for Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human use. ICH guidelines are framed to ensure quality, safety, and efficacy in medicines.

- **Q**-Quality Guidelines This section of guideline covers the (a) effect of different environmental conditions/dosage forms/ Bracketing and Matrixing Designs on the stability of new drug substances and products and evaluation of stability data(b) Procedure for analytical method validation in the stability analysis (c) Information regarding presence of impurities in active pharmaceutical ingredients as well as pharmaceutical finished products.
- **S-**Safety Guidelines. This guideline comprises of safety rules to expose the potential risk like carcinogenicity, genotoxicity, and nephrotoxicity associated with Pharmaceuticals. It suggests in vitro and in vivo pre-clinical studies covering carcinogenic, genotoxic, nephrotoxic and reprotoxic studies.
- **E-** Efficacy Guidelines. This guideline covers clinical safety, Dose-response studies, Good Clinical Practices and clinical evaluation in the human subject.
- **M-**Multidisciplinary Guidelines – These include Medical Terminology, Electronic Standards for Transmission of Regulatory Information, and others that are related to stability.

  Guideline **M4**: The Common Technical Document (CTD)

1.1.3.1 ICH Q-Guidelines (Quality).

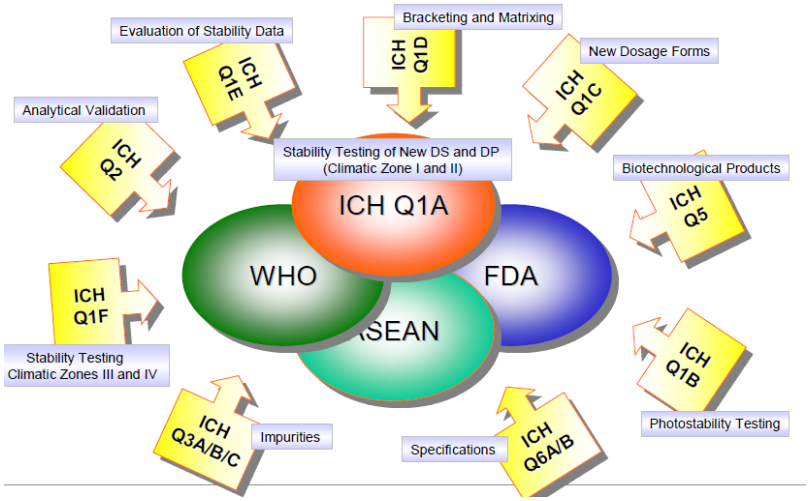


Fig.1. ICH Q-Guidelines overview.

1.1.3.2 ICH Q 1-Guidelines.

Structure/Sections.

1. General

2. Stress Testing

• Comprehensive Stress testing for drug substances

• Icon stability for Drug product

3. Choice of batches

• A minimum of 3 primary batches of the drug substance/Drug product.

4. Instrumentation closure system

5. Specifications/Significant Changes.

A. Drug substance.

• Failure to fulfill the specifications.

B. Drug Product.

• Fifth modification in assay from its initial price.

• Any degradation of product surpassing is the acceptance criteria.

• Failure to fulfill the acceptance criteria for the look, physical attributes, and practically check e.g. color, section separation, suspensibility, caking, hardness, etc..

• Failure to fulfill the acceptance criteria for pH scale

• Failure to fulfill the acceptance criteria for dissolution for 12 dosage units.

6. Testing frequency

A. Long run storage condition.

Frequency ought to be each three months over the first year, every six months over the second year, and annually thenceforth through the projected retest amount(for the drug substance with a proposed re-test period of a minimum of twelve months)

B. Accelerated storage conditions

A minimum of three-point time, together with the initial and final time points(e.g.0,3 and six months), from 6-month study is suggested.

C. Intermediate storage conditions.

When testing at the Intermediate storage conditions is termed for as a result of important modification at the Intermediate storage conditions, a minimum of 4- point, together with the initial and final points(0,6,9,12 months), from a 12 -month study is suggested

7. Storage conditions.

Table.2. Different storage conditions for Drug products - General case.

Types of Study	**Storage Condition as per ICH**	**The minimum time requirement of data submission**
Long term	$25^0C \pm 2^0C/60\ \% \pm 5\%$ RH $30^0C \pm 2^0C/65\ \% \pm 5\%$ RH	12 months
Intermediate	$30^0C \pm 2^0C/65\ \% \pm 5\%$ RH	6 months
Accelerated	$40^0C \pm 2^0C/75\ \% \pm 5\%$ RH	6 months

Table.3. Storage conditions for API and drug product - packaged in semi-permeable containers as per ICH guidelines.

Types of Study	**Storage Condition as per ICH**	**The minimum time requirement of data submission**
Long term	$25^0C \pm 2^0C/40\ \% \pm 5\%$ RH $30^0C \pm 2^0C/35\ \% \pm 5\%$ RH	12 months
Intermediate	$30^0C \pm 2^0C/65\ \% \pm 5\%$ RH	6 months
Accelerated	$40^0C \pm 2^0C/$ NMT 2 5% RH	6 months

Table.4. Storage conditions for API and drug product to be stored in the refrigerator as per ICH guidelines.

Types of Study	Storage Condition as per ICH	The minimum time requirement of data submission
Long term	$5^0C \pm 3^0C$	12 months
Accelerated	$25^0C \pm 2^0C$/60 % ± 5% RH	6 months

Table.5. Storage conditions for API and drug product to be stored in a freezer as per ICH guidelines.

Types of Study	Storage Condition as per ICH	The minimum time requirement of data submission
Long term	$-20^0C \pm 5^0C$	12 months

8. Stability commitments

9. Evaluations/Examinations

10. General Statements/Labelling.

1.2 Impurity [3,4]

The undesirable substances present along with the active pharmaceutical ingredient (API's) or get introduced during the formulation or upon aging of both API and formulated API's to medicines are defined as impurities.

1.2.1 Types of Pharmaceutical Impurities.

Organic impurities (Process & Drug Related): Organic Impurities will arise throughout the manufacturing method and/or storage of the new drug substance. they'll be known or unidentified, volatile or nonvolatile, and includes:

Starting Materials

By-Products

Intermediates

Degradation product

Reagents, ligands, and catalysts

2. Inorganic Impurities: Inorganic impurities may end up from the manufacturing method. They're unremarkably known and identified and include:

Reagents, ligands, and catalysts.

Heavy metals or different residual metals.

Inorganic Salts.

Different materials (e.g., filter aids, charcoal etc).

Residual solvents.

3. Residual solvents: -

A number of solvents (inorganic or organic liquids) ranging from solutions to suspensions are generally used as vehicles for the preparation of different types of formulations along with the preparation of medicinal drugs. Since most of them are found to be associated with more or less toxicity, so, they also are considered as impurities (in some cases) in drug substance or drug product.

1.2.2 Separation of Impurities and Analytical method:

1. HPLC method (photo diode detector)
2. Preparative Chromatography
3. Use of LC-MS, LC-MS/MS sub structural analysis
4. LC-NMR analysis
5. HPTLC
6. Stressed samples of API and product/formulation
7. Aged samples of API and products

1.2.3 International Conference of Harmonization (ICH) Guidelines for Impurity Profile:

ICH provides the investigator with certain guidelines **[Q3B (R2)]** for the analytical procedures for impurity detection, reporting of impurity content of batches and qualification of impurities.

1.3 Packaging [5]

The packaging is the technology of enclosure or protective merchandise for distribution, storage, sale, and use. thus, the packaging is defined because of the collection of various elements that surround the pharmaceutical product from the time of production to its use. Packaging conjointly

protects the fabric against all adverse external influences that can alter the properties of the product.

1.3.1 Type of Packaging:

1. Primary packaging- This is the first envelope which is the direct contact with dosage forms or equipments. The packaging need to be such that there should not be any interaction with drug and should not cause any contaminations in dosage forms E.g Strip package, blister package etc.

2. Secondary packaging- This is the consecutive covering or package which stores pharmaceutical package in it for their grouping, E.g. Cartoon, Boxes etc.

3. Tertiary packaging- This is to provide bulk handling and shipping of the dosage forms from one place to another, Eg. Containers, Barrels etc.

1.3.2 Types of packaging

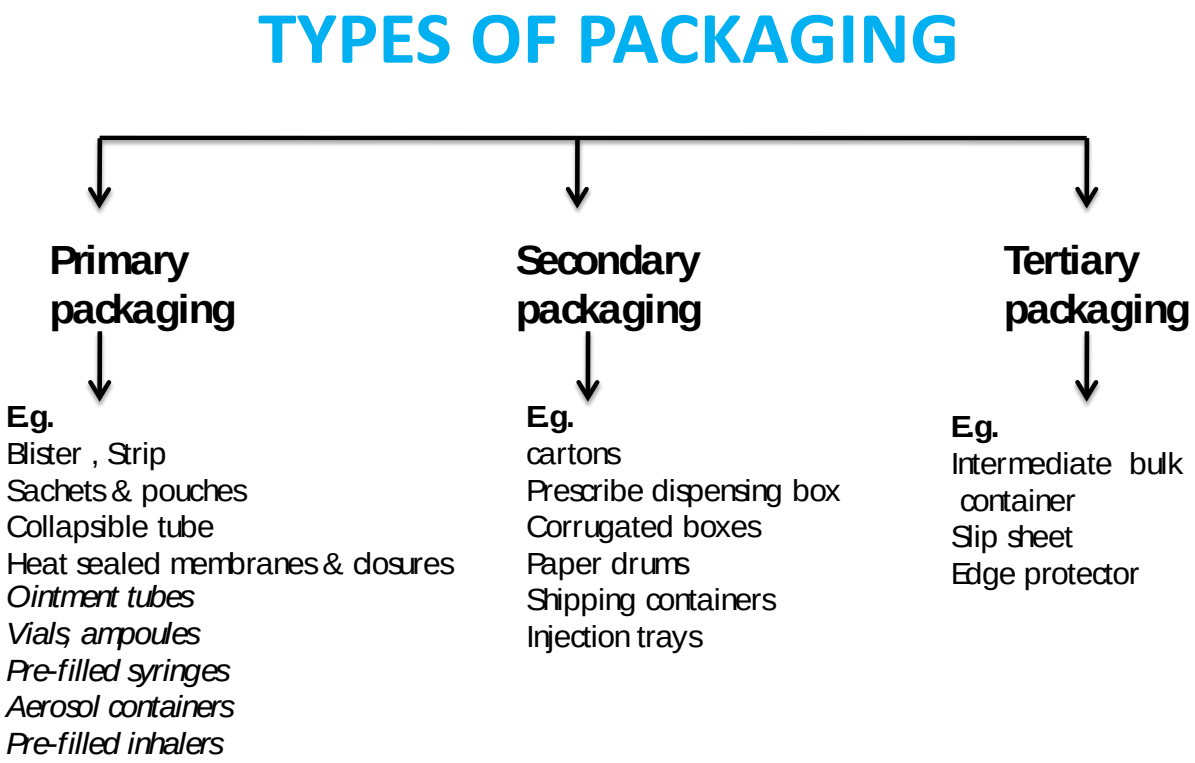


Fig.2. Types of packaging in pharmaceutical industries

1.3.3 Materials used for pharmaceutical packaging:

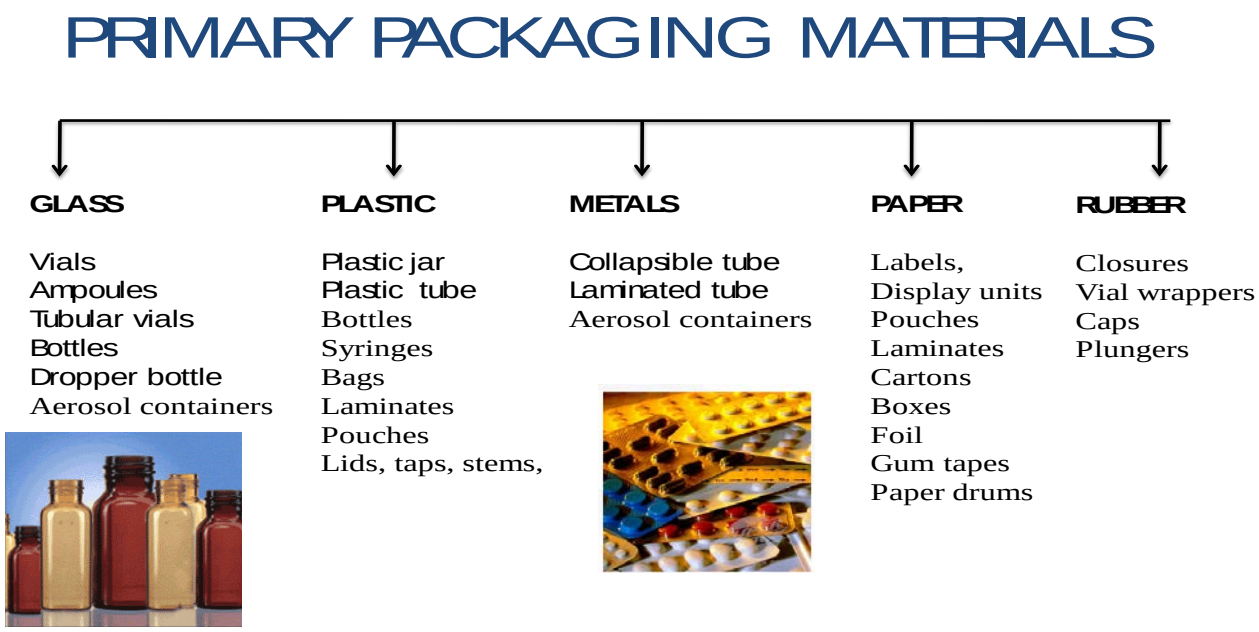


Fig.3. Primary packaging materials used in pharmaceuticals

1.3.3 Primary packaging material and stability of drug product

Stability of the dosage form depends a lot on the type of primary packaging material. The nature of the container-closure system and the properties of the primary packaging material define the stability of the dosage form. Thus, it is important to assess the impurity profile of the dosage form and also evaluate the compatibility of the same with the primary packaging material.

1.4 Validation of analytical Test Method [6]

Method validation is the process or procedure employed to access the performance characteristics of the method under consideration in order to ensure a degree of agreement between test results and true value. It meets the requirements for the intended analytical applications.

1.4.1 Objective of validation:

- To check the quality, reliability, and consistency of results.
- To produce the documented evidence.
- Are the regulatory requirements.

- Identification of sources and quantification of potential errors.

1.4.2 Classes of Analytical Methods:

- Class A: To authenticate the identity
- Class B: To qualify (B_d) and quantify (B_q) impurities
- Class C: To carry out the quantitative analysis of the concentration, or to perform the assay.
- Class D: To evaluate the characteristics.
- Other classes not included in the guides.

Table.6. Different Validation parameter.

USP <1225>	**ICH**	**USFDA**
Accuracy	Accuracy	Accuracy
Precision	Precision	Precision
Repeatability	Repeatability	Repeatability
-	Intermediate Pre.	Intermediate Pre.
Reproducibility	Reproducibility	Reproducibility
Specificity	Specificity	Specificity
LOD	LOD	LOD
LOQ	LOQ	LOQ
Linearity	Linearity	Linearity
Range	Range	Range
Ruggedness	No	No
Robustness	Robustness	Robustness
--	--	Stability of sol.
System Suitability	System Suitability	System Suitability

Chapter 2

Review of Literature

2. LITERATURE REVIEW

Kenneth C. et.al, (2005) [7] explored the methods indicating the chemical stability of pharmaceutical dosage forms with reference to the most important degradation mechanisms usually determined in pharmaceutical development. Applicable strategies to carry out an accelerated aging study of liquid and solid dosage forms, including variation from smallest to the bulky molecule as active pharmaceutical ingredients were decoded. In contrast to chemical stability followed by accelerated aging methods the review also included general thermal methods in relation to reactions like- oxidization, hydrolysis, reaction with reactive excipient impurities, photolysis and macromolecule denaturation.

Vaijanath G. et.al (2007) [8] carried out the characterization and quantitative determination of impurities in piperaquine phosphate bulk drug substance. In total, four impurities were examined by HPLC and LC/MS/MS. The gradient reverse phase HPLC methodology followed by LC/MS/MS was done. Spectroscopically study -IR and NMR were further carried out to confirm the structures of the impurities. The strategy was found to be quite specific, accurate, precise and linear as suggested in ICH guidelines. Furthermore, forced degradation studies of the piperaquine phosphate bulk drug samples were also performed to establish the stability indicating the power of the recently developed HPLC methodology.

Anthony B. Ciavarella et.al (2007) [9] developed a valid HPLC methodology for the analysis of gabapentin along with 3,3-pentamethylene-4-butyrolactam that is the major impurity found in the medicine. A simple procedure based on reversed-phase HPLC technique that was isocratic in nature was established and authenticated to analyses the different dosage forms- capsules and tablets of gabapentin and its major deteriorated impurity. The Brownlee Sphere-5 Cyano was used as column separator while acetonitrile-10millimoles Potassium dihydrogen phosphate/ /10millimoles Dipotassium hydrogen phosphate (pH 6.2) (8:92, v/v) was used as mobile phase. The flow rate was kept at 1ml/min and the compounds were eluted. The mode of elution was isocratically followed by detection the compounds with ultraviolet detection at 210 nm. This technique was in accordance with USP category -I and USP Category-II for gabapentin and 3,3-pentamethylene-4-butyrolactam respectively. The characteristic like accuracy, precision, specificity, range, linearity, the limit of quantitation and robustness were met throughout the work and outlined the standards of validation. The quality examination of four samples of gabapentin was carried out successfully with his technique.

Sidika E, et.al (2003) [10] established an efficient HPLC method for the quantification of atorvastatin as a drug. Different forms of atorvastatin- bulk drug and tablets along with impurities present within were successfully detected. The good resolution was observed for atorvastatin, diastereomer-atorvastatin, fluoro-atorvastatin, indefinite impurities and formulation excipients of tablets. Ultraviolet detection following a gradient reverse-phase HPLC technique was used for the detection of the atorvastatin and its impurities in bulk drug and tablets. The solvents with varying pH scale values like a wood spirit or acetonitrile and water or buffer systems were used as a solvent used in this experiment. The column utilized for the separation was Luna C18 column along with acetonitrile-ammonium acetate buffer pH scale 4-tetrahydrofuran as a mobile phase. To obtain the best resolution the flow rate of 1.0 ml/min was maintained. The mode of elution was kept gradient followed by detection at 248 nm. The result of the analysis included the varying amount of impurities -0.057-0.081, 0.072-0.097, 0.608-0.664% of the diastereomer-atorvastatin, des-fluoro-atorvastatin, and total impurity, respectively

Fabrice Krier et.al (2011) [11] focused on a new technique employing a rapid sub-2µm column. for the separation of Clinoril and of its three connected impurities The study was based aspects various aspects including -Length of the primary isocratic phase, the proportion of organic modifier at the start and end of the gradient and the gradient time. The optimum condition resulted in the separation to take place in 6 min. Lastly, the accuracy profile approach was effectively applied to validate the strategy in order to determine its ability to accurately carry out the quantification of drug products.

Dunge A, et.al (2005) [12] established a specific HPLC technique for analysis of zidovudine throughout stability studies. The study was aimed to develop a valid stability-indicating assay technique for ZDV once subjecting it to forced decomposition under oxidization, hydrolysis, photolysis, and thermal stress conditions. The drug decomposed under hydrolytic stress upon refluxing and exposure to light, and it had been stable to oxidation and thermal stress. the main decomposition product may be seen all told the decomposed solutions, that was known as thymine through comparison with the quality. The major and minor degradation products of the drug along with the main drug were efficaciously isolated utilizing the technique. The method involved the use of C-18 as the column and water-methanol in the ratio of 77:23 as mobile phase. The detection wavelength was selected as 265 nm. The report of the analysis indicated that the procedure was validated in respect to linearity with the amount of drug ranging from 25-

500 microgram/milliliters. The result of the study indicated 21,859 (±0.213) and 0.9995 (±0.00578) as the mean values (±R.S.D.) of slope and correlation. The Relative standard deviations values were found to be are relative to intra and inter-day study.

Barbas at.al (2005) [13] carried out separations of Acyclovir, guanine, and impurity A that were isocratic in nature. The pH scale was kept at 3.0 and the mobile phase was made to run along the SB-CN column for 15 min. The column was from Agilent (150millimetres×4.6millimetres and 3.5metres). Furthermore, on raising the run time to 40 min isolation of guanine, acyclovir along with six variable impurities was observed. The buffer A/acetonitrile 96:4 (v/v), being buffer A: 25millimole H3PO4 (Milli-Q H2O) adjusted to weak acidic pH scale of 3.0 with Potassium hydroxide was used in the procedure. Isolation of drug from all of the impurities denoted in the pharmacopeia, together with impurity C, that eluted along with drug product within the preceding situations with a mobile phase prepared with 25millimoles orthophosphoric acid (pH scale 1.8)/acetonitrile 96:4 (v/v) was carried out utilizing the same column. ICH guidelines were followed for the method validation and confirmed to be reliable for drug product and its impurities determination.

Changqin Hu et.al (2014) [14] developed a systematic study with the aim to improve the safety and quality of cefpodoxime proxetil. The technique was based on Reversed-phase liquid chromatography methodology to characterize impurities in cefpodoxime proxetil, an ester-modified prodrug. The technique included liquid chromatography in association with electrospray ionization tandem mass spectroscopy (ESI-MS/MS) that supported the mechanisms by which cephalosporins are degraded, stress tests were designed and performed. The formic acid–methanol-water were used as the mobile section and the C18 column was used to elute the bulk material and capsule. Seven established impurities and eight new impurities present within commercial samples were characterized. The fragmentation patterns of cefpodoxime proxetil were used as a standard to identify those unknown compounds. Data from this can facilitate

Hayam Mahmoud Lotfy (2010) [15] conferred two stability-indicating methods. These methods were based on sensitive, selective and precise strategies for the determination of ACV in the presence of its degradation product (Guanine) either in bulk powder or in pharmaceutical formulation. Statistical analysis of the results was also carried out revealing high accuracy and smart precision. The first method utilized the derivative of the ratio spectrophotometry (DD1) by measurement of the amplitude at 265 nm. The second method B relied on a high-performance

liquid chromatographical (HPLC) separation of ACV from its degradation product exploitation an ODS column with a mobile part consisting of acetonitrile. Distilled water (4:96, v/v,) with UV detection at 254 nm. The multivariate study indicated sensible correlation within the concentration ranges 10-60 µgmL-1 and 20-120 µgmL-1with percentage recoveries of 100.06±0.89and 99.62±0.66 for the first and second method, respectively.

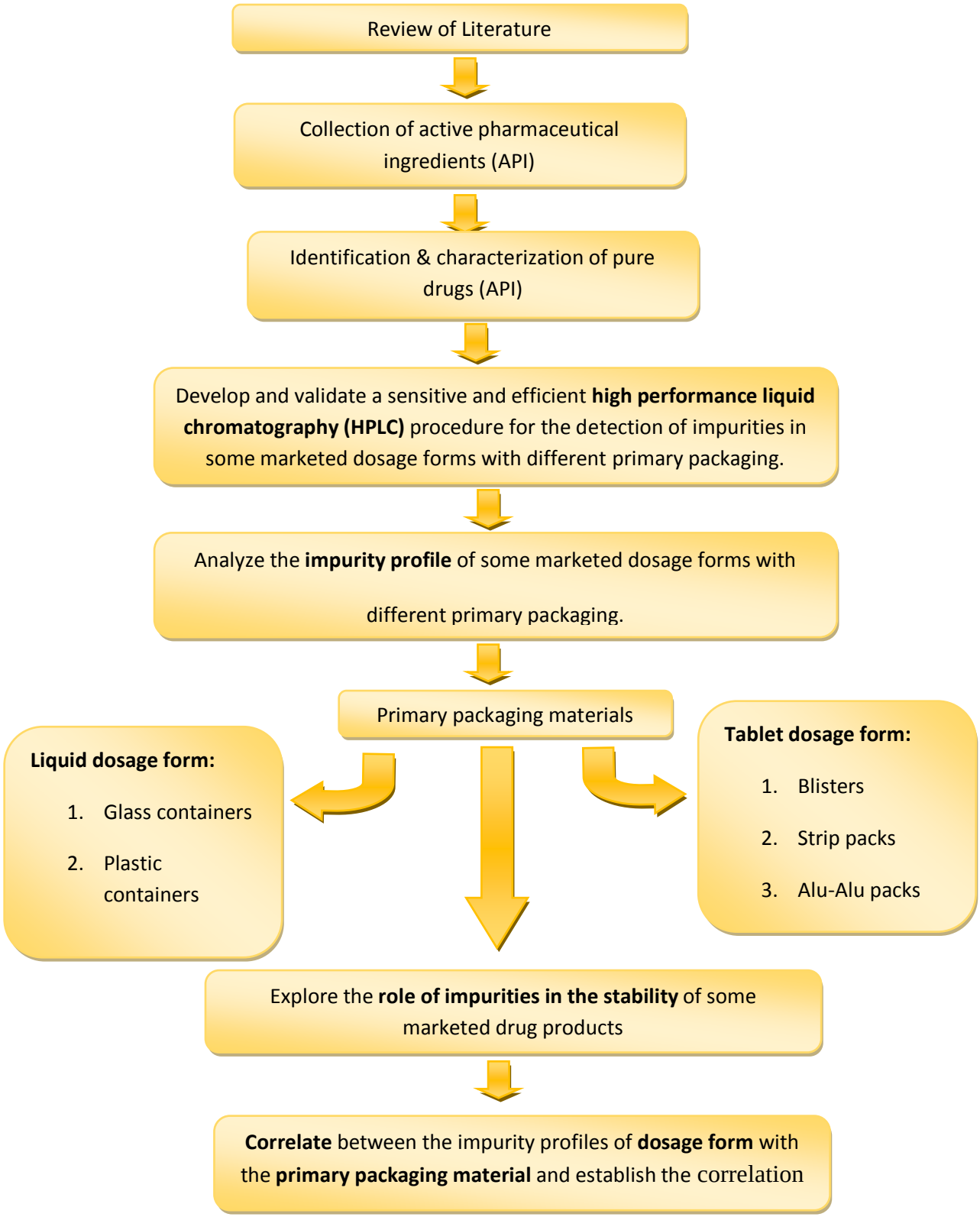
Chapter 3

Aim & Objective

3. AIM & OBJECTIVE.

1. To develop and validate a sensitive and efficient **high-performance liquid chromatography (HPLC)** procedure for the detection of impurities in some marketed dosage forms with different primary packaging.
2. To analyze the **impurity profile** of some marketed dosage forms with different primary packaging.
3. To explore the **role of impurities in the stability** of some marketed drug products.
4. To **correlate** between the impurity profiles of the **dosage form** with the **primary packaging material** and establish the correlation, if any, exists between them.

4. Research Methodology


Review of Literature
Collection of active pharmaceutical ingredients (API)
Identification & characterization of pure drugs (API)
Develop and validate a sensitive and efficient high performance liquid chromatography (HPLC) procedure for the detection of impurities in some marketed dosage forms with different primary packaging.
Analyze the impurity profile of some marketed dosage forms with different primary packaging.
Primary packaging materials
Liquid dosage form:
1. Glass containers
2. Plastic containers
Tablet dosage form:
1. Blisters
2. Strip packs
3. Alu-Alu packs
Explore the role of impurities in the stability of some marketed drug products
Correlate between the impurity profiles of dosage form with the primary packaging material and establish the correlation

Chapter 4

Materials and Methods

4. MATERIAL & METHODS.

4.1 Material:

Table.7. List of the instrument.

S. No.	Instrument/ Equipment Name	Make and Models of Instruments/Equipment
1	HPLC	Agilent prominence Diode array detector System Software (Agilent Empower)
5	Micro Balance	Mettler Toledo
6	Weighing Balance	Mettler AE240
7	Water Bath	High Precision Water Bath with digital temperature controller
8	Sonicator	Power-Sonic 410
9	Stability Oven	

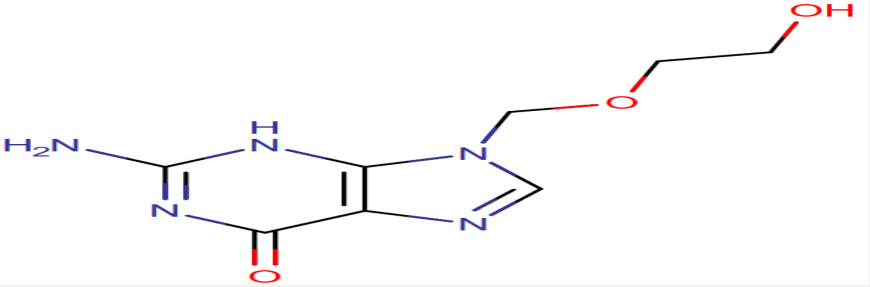
Chapter 5

Drugs Profile

3.1. Drugs profile [16-18]

3.1.1. Drug profile of Acyclovir

Table 5.1: Drug profile of Acyclovir

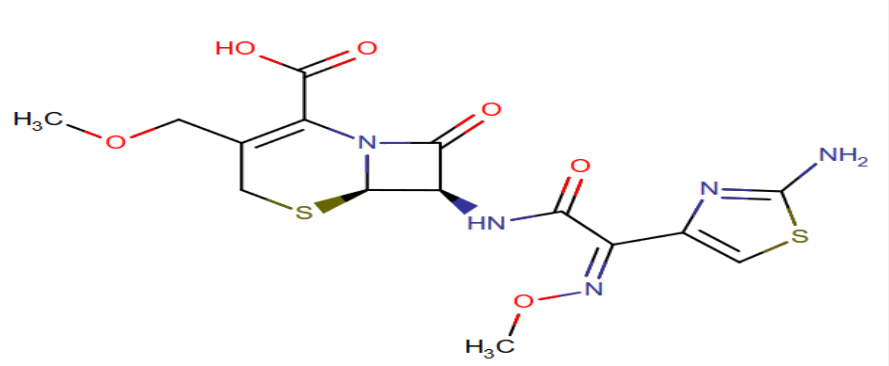
Name	Acyclovir
Type	Drug molecule
Description	Aciclovir is a guanosine derivative and a potent antiviral drug with low toxicity. The drug can be used for the treatment of herpes simplex virus infections. The drug is also investigated for the treatment of herpes simplex using the iontophoretic device. Because of its limited penetration through the skin it show a low level of efficacy in the treatment of cold sores.
Structure	
Weight	227
Chemical Formula	$C_8H_{11}N_5O_3$
Pharmacology	
Indication	Acyclovir is used in the treatment of herpes zoster, genital herpes and also in chickenpox.
Mechanism of action	The drug is phosphorylated by viral-specific thymidine kinase to monophosphate derivative. Further phosphorylation by host cell kinase leads to the formation of acyclovir triphosphate, which inhibits viral DNA synthesis. The antiviral spectrum includes Herpes simplex virus (HSV) 1 and 2, Varicella zoster virus (VZV) and

	Epstein barr virus (EBV). HSV and VZV can develop resistance to acyclovir, particularly in HIV positive patients.
Absorption	Given orally, it has a bioavailability of 15-30% the CSF level of the drug is 50% that of plasma. Hence, for viral encephalitis, it is given IV. Its t½ is for 3 hours. It is mostly excreted unchanged in the urine; 15% is metabolized in the liver.
Protein binding	9 to 33%
Metabolism	15% is metabolized in the liver
Route of elimination	It is mostly excreted unchanged in the urine
Half-life	2.5-3.3 hours
Toxicity	Locally it may cause stinging and reversible superficial keratopathy. Orally, the drug is generally well tolerated. Given IV, it may cause headache, thrombophlebitis, and elevation of blood urea and creatinine (*crystalline nephropathy*). CNS toxicity includes delirium, tremors, abnormal EEG and hallucinations (*Neuropsychiatric reaction*).

5.1.1 Drug profile of Cefpodoxime

Table 5.2: Drug profile of Cefpodoxime

Name	**Cefpodoxime**
Type	Small molecule
Description	It is a third generation oral cephalosporin antibiotic. The drug shows high effectiveness against gram negative and gram-positive bacteria. Cefpodoxime is commonly used for the treatment of acute infections like pharyngitis, sinusitis, otitis media. Cefpodoxime proxetil is a prodrug that is de-esterified in intestinal mucosa and also absorbed in the intestine.

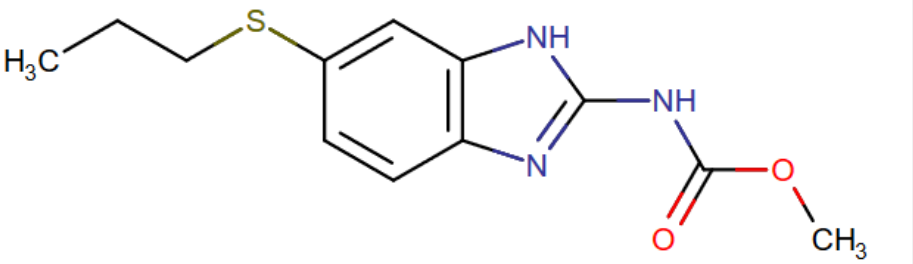
Structure	
Weight	427.56
Chemical Formula	$C_{15}H_{17}N_5O_6S_2$
Pharmacology	
Indication	Cefpodoxime is used in the treatment of various gram-positive and gram-negative mild to moderate infections caused by vulnerable strains.
Pharmacodynamics	The drug shows effectiveness against a broad class of gram-positive and gram-negative bacteria. However, the drug is found less effective against aeruginosa, Enterococcus, and Bacteroides.
Mechanism of action	Cephalosporins act by inhibiting bacterial cell wall synthesis in a manner similar to penicillins and are bactericidal. Resistance to cephalosporins develops slowly and is mediated either by bacterial beta-lactamases or by lack of bacterial permeability to the drug. Cross-resistance for other beta-lactam agents also occurs.
Absorption	Cefpodoxime proxetil is a prodrug which absorbed from gastro-intestinal tract and causes de-esterification to convert it into active form cefpodoxime. As with penicillins, cephalosporins are administered either orally or IV; IM administration is painful. Their body distribution is similar to that of penicillin. There are significant differences among the various cephalosporins regarding

	their pharmacokinetics.
Volume of distribution	NA
Protein binding	22 to 33% in blood serum and from 21 to 29% in blood plasma.
Metabolism	Liver in case of the oral route
Route of elimination	Cephalosporins are eliminated mainly by renal tubular secretion and high concentrations are achieved in the urinary tract. Renal tubular blocking with probenecid increases the plasma levels significantly. The renal excretion is markedly reduced in renal insufficiency. Therefore their dose should be appropriately reduced in case of renal impairment. Concentration in the bile is similar to that in the plasma. Unlike other cephalosporins, the drug is partly metabolized by the liver before excretion by the kidneys.
Half-life	2.09 to 2.84 hrs
Clearance	NA
Toxicity	Skin rash, fever, serum sickness, anaphylactoid reaction (rare), eosinophilia, neutropenia, transient splenomegaly, and increased SGOT levels.

5.1.2 Drug profile of Albendaloze

Table 5.3: Drug profile of Albendazole

Name	Albendazole
Type	Drug molecule
Description	This broad spectrum benzimidazole has actions similar to those of mebendazole. It also has larvicidal actions in hydatid disease, ascariasis and ankylostomiasis and ovicidal properties in ascariasis, ankylostomiasis, and trichuriasis.

Structure	
Weight	265.33
Chemical Formula	$C_{12}H_{15}N_3O_2S$
Category	Anthelmintic.
Mechanism of action	The drug causes serious changes in the skin and intestinal cells of the intestinal worms which cause a decrease in the energy production results in immobilization and death of the parasite.
Absorption	Given orally, it is rapidly absorbed and has better bioavailability than mebendazole. After absorption, it undergoes first-pass metabolism in the liver to its active metabolite, albendazole sulfoxide
Protein binding	70% bound to protein
Metabolism	Liver
Route of elimination	Renal excretion
Dose	Nematode infestation, 400 mg as a single dose; cestodal infestation, 400 mg daily for three consecutive days; strongyloidiasis, 400 mg daily for three consecutive days.
Clearance	NA
Toxicity	These are usually mild and include GI disturbances, abdominal pain, headache, drowsiness and skin rashes.

6 REFERENCES.

1. Stability Testing of New Active Substances and Medicinal Products, ICH Topic Q1A. ICH Harmonized Tripartite Guidelines, ICH, Surrey, U.K., 1996, CPMP/ICH/280/95.
2. https://www.ich.org/products/guidelines/quality/article/quality-guidelines.html
3. ICH Q3A (R2) impurities in new drug substances, ICH, October 2006, published in the Federal Register, 14 November 2003, Vol, 68, No. 220, p. 64628-9.
4. Impurities, ICH Q3B (R2) impurities in new drug products, ICH, October 2006, published in the Federal Register on June 2008.
5. Pareek V, Khunteta A. Original Article PHARMACEUTICAL PACKAGING : CURRENT TRENDS AND FUTURE. 2014;6(6).
6. ICH Q2(R1) Validation of analytical procedures, ICH, November 1996, Published in the Federal Register, 1 March 1995, Vol. 60, p. 11260
7. Waterman KC, Adami RC. Accelerated aging : Prediction of chemical stability of pharmaceuticals Accelerated aging : Prediction of chemical stability of pharmaceuticals. 2018;(September).
8. Dongre VG, Karmuse PP, Ghugare PD, Gupta M, Nerurkar B, Shaha C, et al. Characterization and quantitative determination of impurities in piperaquine phosphate by HPLC and LC / MS / MS. 2007;43:186–95.
9. Ciavarella AB, Gupta A, Sayeed VA, Khan MA, Faustino PJ. Development and application of a validated HPLC method for the determination of gabapentin and its major degradation impurity in drug products &. 2007;43:1647–53.
10. Ertu S. An HPLC method for the determination of ator v astatin and its impurities in bulk drug and tablets. 2003;33:1017–23.
11. Krier F, Brion M, Debrus B, Lebrun P, Driesen A, Ziemons E, et al. Journal of Pharmaceutical and Biomedical Analysis Optimisation and validation of a fast HPLC method for the quantification of sulindac and its related impurities. J Pharm Biomed Anal [Internet]. 2011;54(4):694–700.
12. Dunge A, Sharda N, Singh B, Singh S. Validated specific HPLC method for determination of zidovudine during stability studies. 2005;37:1109–14.
13. Barbas C. LC methods for acyclovir and related impurities determination. Journal of Pharmaceutical and Biomedical Analysis 37 2005;37:687–94.

14. Li J, Zhang D, Hu C. Characterization of impurities in cefpodoxime proxetil using LC – MS n. Acta Pharm Sin B [Internet]. 2014;4(4):322–32.
15. K PA, Campus SK. Method for estimation of ivermectin and albendazole in pharmaceutical dosage forms. Indian Journal of Drugs, 2015, 3(3), 57-702015;3(3):57–70.
16. Indian pharmacopoeia-2014, Indian pharmacopoeia commission. Ghaziabad, Vol. 3; 570-571
17. United States Pharmacopeia (2007), National Formulary, Rockville, MD, 152.
18. https://www.drugs.com/ last acssed on 30/05/2019

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